

*TOLERANCE TO THE EFFECTS OF  
COCAINE ON PERFORMANCE UNDER  
BEHAVIOR-CORRELATED REINFORCEMENT MAGNITUDE*

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Four pigeons responded under a fixed-interval 8-min schedule of food delivery in which the amount of food delivered at the end of each interval depended on performance during the interval (i.e., a correlated schedule). Specifically, duration of access to grain was contingent upon the number of responses made during the first 4 min of the interval. This differential outcome did not affect response rates or patterning relative to performance under a simple fixed-interval 8-min schedule. Behavior under the correlated schedule was then investigated under doses of cocaine ranging from 0.3 to 10.0 mg/kg. A bitonic dose-response function was obtained for response rates and the time with head in the food hopper, whereas dose-dependent decreases were observed in the mathematical index of curvature (Fry, Kelleher, & Cook, 1960). The dose that produced the greatest increase in the head-in-hopper time was then administered prior to each session. Following repeated administration of cocaine, disruptions in response patterning were attenuated for all 4 pigeons; tolerance was also observed to the rate-increasing effects and increased head-in-hopper time for 2 pigeons after chronic cocaine administration. Tolerance therefore developed despite the fact that the initial effect of cocaine was to increase the amount of food obtained.

*Key words:* fixed-interval schedule, cocaine, tolerance, reinforcement loss, correlated schedule, key peck, pigeons

Tolerance is characterized by a reduction in the potency of a drug in producing an effect after repeated administration, and can be measured in terms of changes in operant performance. Tolerance to the effects of cocaine on operant performance has been observed under several conditions of response-dependent reinforcement (e.g., Branch, Walker, & Brodkorb, 1998; Hoffman, Branch, & Sizemore, 1987; Hughes & Branch, 1991; Poling & Nickel, 1993; Schama & Branch, 1994; Smith, 1990; Stafford & Branch, 1996; van Haaren & Anderson, 1994).

An influential view of how behavioral factors can influence the development of tolerance is the reinforcement-loss hypothesis (Schuster & Zimmerman, 1961), which states that tolerance is more likely to develop if de-

creased reinforcement rate results from the initial drug effect. For example, Schuster, Dockens, and Woods (1966) observed rats' performance on a two-component multiple schedule first under acute (once every few days) and then under chronic (daily) amphetamine administration. In one component, reinforcement was delivered contingent upon a response after a fixed interval of time had elapsed; in the other component, low response rates were differentially reinforced. In every case in which the acute effect of the drug decreased reinforcement rate, chronic administration of amphetamine resulted in tolerance. These results support the view that tolerance develops when the initial effect of a drug results in a loss of reinforcement, and data in support of this view are abundant (see reviews by Corfield-Sumner & Stolerman, 1978; Wolgin, 1989).

Although a correspondence between reinforcement loss and tolerance has been empirically demonstrated, there are also reports of no tolerance despite an initial loss of reinforcement (H. Brown, 1965; Demellweek & Goudie, 1981; Harris & Snell, 1980; Hoffman et al., 1987; Hughes & Branch, 1991), tolerance without obvious reinforcement loss (Branch, 1979; Schama & Branch, 1994), and tolerance despite increases in reinforcement

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(Branch *et al.*, 1998). In the study by Branch *et al.*, pigeons responded under fixed-ratio (FR) schedules of reinforcement. Acute administration of cocaine increased response rates and, consequently, increased reinforcement rate for 3 of the original 7 pigeons. With daily administration of the rate-increasing dose, a decrease in response rates was observed for each pigeon; thus, tolerance occurred despite the initial increases in reinforcement rate. The opportunity, however, to study the effects of repeated drug administration when the drug initially increased reinforcement was limited to these 3 pigeons.

The present study attempted to find a method by which the interaction of a drug with a schedule can consistently increase the amount of reinforcement delivered to the pigeon. Because cocaine and other psychomotor stimulants increase response rates early in the interval when fixed-interval (FI) schedules are employed (e.g., Branch, 1979; McMillan, 1968a, 1968b, 1969), a behavior-correlated schedule of reinforcement in which reinforcement magnitude was contingent on early-interval responding was used.

In behavior-correlated schedules of reinforcement, the amount of each reinforcer is contingent upon some aspect of the subject's performance (Dodd, 1980; Gentry & Eskew, 1984; Hendry, 1962; Hendry & Van-Toller, 1964). Although few investigations of such schedules have been conducted, each has provided evidence that such arrangements can influence behavior in predictable ways. For example, Gentry and Eskew showed that response rates were sensitive to increased reinforcer magnitude when a direct relation was established between number of responses and duration of access to grain. In this study, pigeons were initially trained to key peck using an automaintenance procedure (cf. Williams & Williams, 1969). Once key pecking was reliably established, a correlated-schedule procedure was implemented in which each response emitted during the 8-s trial generated 0.25-s access to grain delivered at the end of the trial. The number of responses per trial increased relative to control (automaintenance) conditions in which access to grain was held constant. Dodd reported a similar result.

The purposes of the present experiment were (a) to develop a procedure in which co-

caine administration produces reliable increases in the amount of reinforcement obtained; (b) to determine if the addition of a correlated outcome to an FI schedule alters performance under that schedule; (c) to determine whether the acute effects of cocaine on response patterning, rates, and reinforcement magnitude were altered by the presence or absence of the correlated schedule; (d) to investigate the effects of cocaine and behavior-correlated reinforcement magnitude on aspects of FI maintained responding; and (e) to investigate how these relations might contribute to the development of tolerance.

## METHOD

### *Subjects*

Four experimentally naive adult White Carneau pigeons (sex unknown) were maintained at 80% of their ad libitum weights. The pigeons were individually housed in stainless steel cages in a temperature-controlled colony room under a 16:8 hr light/dark cycle. Continuous access to vitamin-enriched water and health grit was made available to the pigeons in their home cages.

### *Apparatus*

Sessions were conducted in a BRS/LVE operant conditioning chamber for pigeons, with dimensions 30.7 cm wide by 35.2 cm high by 35.2 cm deep. The walls and ceiling of the chamber were painted white except for the work panel, which was brushed aluminum and was equipped with three response keys, a food aperture, and a houselight. The response keys were 2.6 cm in diameter, horizontally aligned, and centered 24 cm above the floor. The keys could be transilluminated. Only the center key, transilluminated white by a 1.1-W 28-VDC lamp, was used, and a static force of approximately 0.18 N produced a 30-ms tone and registered as a response. The houselight was a 1.1-W 28-VDC lamp located at the top of the instrument panel 31.1 cm from the floor behind an aluminum shield that deflected light toward the ceiling. Mixed grain was made available through an aperture (5.8 cm by 6 cm) located below the center key and 10 cm above the floor. When grain was available the houselight and keylight were off, and the aperture was illuminated with a

1.1-W 28-VDC lamp. The chamber floor was comprised of steel mesh and the back wall of the chamber was equipped with a ventilation fan that operated continuously during the experimental sessions. White masking noise (approximately 95 dB) was also continuously present in the room in which the chamber was located. The pigeon could be observed through a half-silvered glass (16.5 cm by 19 cm) located in the door of the chamber.

All contingencies were programmed and data collected by a custom-built computer operated under the ECRBasic control system (Walter & Palya, 1984), which in turn interfaced with an IBM-compatible computer located in an adjacent room. In later parts of the study, a MED Associates Single I/R Control generated an infrared beam across the opening of the magazine aperture. This enabled us to obtain a measure of total time that the pigeon's head was in the hopper. A Gerbrands Model C-3 cumulative-response recorder provided continuous recording of responses.

#### *Procedure*

Experimental sessions were conducted 7 days per week between the hours of 8:00 a.m. and 3:00 p.m., at about the same time for each pigeon. Each session was preceded by a 5-min blackout in which all lights in the chamber were off and no programmed contingencies were in effect. After that, the houselight and keylight were illuminated to begin the session.

#### *Training Phase*

Magazine training was completed in three sessions for each pigeon, at which time eating from the raised hopper occurred reliably. These sessions provided 90 4-s opportunities to eat grain from the hopper. Subsequently, pecks to an illuminated key on the work panel were autoshaped (P. L. Brown & Jenkins, 1968); after three sessions of autoshaping, key pecking reliably occurred in the presence of the illuminated key. Thereafter, FI training was implemented; FI values were gradually increased from 1 s to 8 min over the course of 11 sessions. Sessions 1 through 9 were terminated after 25 food presentations. All subsequent sessions were terminated after completion of 10 intervals or after 90 min had elapsed, whichever occurred first.

After 56, 57, 56, and 53 sessions of FI 8-min training for Pigeons 3340, 3658, 6164, and 3578, respectively, typical FI patterning was not observed (i.e., postreinforcement pauses [PRPs] remained short); therefore, a 15-s timeout (all lights out) was introduced after each reinforcer delivery to enhance FI patterning (cf. Ferster & Skinner, 1957, pp. 185 ff.). Subsequently, PRPs increased and cumulative records were more scalloped in appearance.

#### *Phase 1: Baseline (Fixed Reinforcer Durations)*

During this phase, responding was reinforced with 4-s access to grain according to an FI 8-min schedule of reinforcement. If the pigeon completed all 10 intervals, the maximum overall access to grain in that session was 40 s. Performance was judged to be stable when no systematic trends were observed in overall response rates and PRPs. This phase lasted for  $130 \pm 1$  sessions for each pigeon. At this point, an acute dosing regimen was implemented.

#### *Phase 2: Determination of Acute Dose Effects of Cocaine on Simple FI 8 Min*

Cocaine hydrochloride was dissolved in 0.9% sodium chloride solution (saline). Weekly administrations of a range of doses of cocaine (0.3 to 10.0 mg/kg, expressed as the salt) were delivered intramuscularly into each pigeon's breast immediately before placement in the experimental chamber. Each dose was administered at least twice, and injections were separated by at least 6 days. Doses were administered in the following descending series: saline, 10.0 mg/kg, 5.6 mg/kg, 3.0 mg/kg, 1.0 mg/kg, and 0.3 mg/kg. A fixed order was used to facilitate detection of systematic differences across repeated determinations of effects of each dose (see Sidman, 1960). Following two iterations of the descending series, effects of doses that revealed sufficient variability were reassessed until the effects at those doses were replicated. The acute dosing regimen lasted for 54, 78, 108, and 77 sessions for Pigeons 3340, 3658, 6164, and 3578, respectively. Table 1 shows the number of administrations of each dose.

Immediately following the assessment of

Table 1

Number of drug and saline administrations for each pigeon. Numbers in parentheses indicate the number of administrations after measurement of time in hopper began.

Pigeon	Dose of cocaine (mg/kg)	Phase 2: Acute/BL <sup>a</sup>	Phase 4: Acute/C <sup>b</sup>	Phase 5: Chronic/C	Phase 6: Chronic/C	Phase 7: Saline/C
3340	Saline	2	3 (2)	3		111
	0.3	2	3 (2)	2		2
	1.0	2	4 (2)	2		2
	3.0	2	3 (2)	106		2
	5.6	2	4 (3)	2		2
3658	Saline	2	3 (2)	3		96
	0.3	2	3 (2)	2		3
	1.0	2	4 (2)	2		3
	3.0	4	4 (2)	114		2
	5.6	2	4 (2)	2		3
6164	Saline	3	3 (2)	3	3	109
	0.3	2	4 (3)	2	2	2
	1.0	3	3 (2)	105	2	2
	3.0	4	3 (2)	2	112	2
	5.6	3	4 (2)	2	2	2
3578	10.0	2	3 (0)	0	0	0
	Saline	3	3 (3)	3	2	131
	0.3	0	3 (0)	2	3	2
	1.0	2	5 (3)	2	2	2
	3.0	3	3 (2)	196	2	2
	5.6	3	3 (2)	2	4	2
	10.0	2	3 (1)	2	128	2

<sup>a</sup> Baseline FI 8-min schedule.

<sup>b</sup> Correlated schedule.

the effects of the various doses of cocaine, the pigeons continued to perform without drugs on the FI until performance was again stable. This phase lasted 75, 60, 33, and 60 sessions for Pigeons 3340, 3658, 6164, and 3578, respectively. The correlated schedule of reinforcement then was implemented.

### *Phase 3: Correlated Schedule of Reinforcement*

During this condition, duration of access to grain was correlated with early-interval responding during the FI 8-min schedule. Responses emitted during the first 4 min of the 8-min interval determined the amount of reinforcement to be delivered at the end of that interval. Feeder presentation durations of 2 s, 4 s, and 8 s were used. The total number of responses required in the first half of the interval to earn the different feeder durations was determined individually based on each pigeon's performance in the baseline phase (Phase 1). Rate requirements were chosen such that initially each pigeon would be likely to encounter each of the feeder durations an equal number of times in a session.

This was accomplished by determining the total number of responses occurring in the first 4 min of each interval over the last 10 sessions (i.e., last 100 repetitions of the FI) of the baseline phase. The largest value obtained was subsequently used as the basis for establishing a frequency distribution for each pigeon, which consisted of 10 equal-width class intervals with each interval being one 10th the largest value. Cutoff values were set at (a) below the 33rd percentile, (b) between the 33rd and 66th percentiles, and (c) above the 66th percentile of the resulting distribution. Exact percentile values were determined by linear interpolation. Duration of access to grain then was made to depend on the number of responses in the first half of each interval such that higher rates of responding early in the interval yielded longer access times. For example, if the total number of responses in the first half of the interval (R) was less than 18 (the 33rd percentile) for Pigeon 3340, then 2-s access to grain was delivered upon completion of the interval. If the number of responses ranged from 18 to 74 during this period, grain delivery was 4 s.

More than 74 responses yielded an 8-s feeder duration. For the other 3 pigeons, criteria for obtaining 2-s, 4-s, and 8-s feeder durations, respectively, were as follows:  $R < 15$ ,  $15 \leq R \leq 59$ ,  $R > 59$  (Pigeon 3658);  $R < 18$ ,  $18 \leq R \leq 55$ ,  $R > 55$  (Pigeon 6164); and  $R < 18$ ,  $18 \leq R \leq 63$ ,  $R > 63$  (Pigeon 3578). After 52 to 53 sessions, performance was judged to be stable, and the correlated-schedule phase without cocaine administration ended.

*Phase 4: Determination of Acute Drug Effects under the Correlated Schedule*

A range of doses of cocaine (0.3, 1.0, 3.0, 5.6, and 10.0 mg/kg) was administered once per week prior to experimental sessions. The drug regimen was procedurally identical to the acute dosing regimen previously described for Phase 2. In addition, after 65 to 67 sessions in this phase, installation of an infrared beam across the aperture allowed collection of head-in-hopper times (i.e., times between entry and exit). Thereafter, stability was based on a lack of systematic trends in response rates, PRPs, index of curvature, and head-in-hopper times. The acute dosing regimen in this phase lasted for 136, 129, 142, and 163 sessions for Pigeons 3340, 3658, 6164, and 3578, respectively. After the determination of acute drug effects, the pigeons received daily presession injections of saline for 7 days.

*Phase 5: Determination of Chronic Drug Effects under the Correlated Schedule*

The effects of chronic administration of cocaine were assessed by injecting Pigeons 3340, 3658, and 3578 with 3.0 mg/kg of cocaine and Pigeon 6164 with 1.0 mg/kg of cocaine prior to each experimental session. These doses were selected because acutely, during Phase 4, they increased head-in-hopper times (i.e., they produced the most "reinforcement gain"). This regimen continued until session-to-session performance was stable, which occurred within 65, 62, 54, and 55 sessions for Pigeons 3340, 3658, 6164, and 3578, respectively. Daily drug administrations continued after performance stabilized, and other doses of cocaine and saline were substituted no more often than once per week for the chronic dose, with each other dose

tested at least twice. Numbers of administrations of each dose during determination of acute and chronic effects are shown in Table 1.

*Phase 6: Assessment of Increased Dosages During Chronic Administration under the Correlated Schedule*

Immediately after the assessment of chronic dosing effects, 2 pigeons, because of interesting features of their data, were subjected to additional experimentation. The chronic phase was continued for Pigeons 6164 and 3578, with doses of cocaine increased to 3.0 mg/kg (from 1.0 mg/kg) and 10.0 mg/kg (from 3.0 mg/kg), respectively. Stability was obtained within 51 and 57 sessions for Pigeons 6164 and 3578, respectively. At this time a range of doses (0.3, 1.0, 3.0, 5.6, and 10.0 mg/kg) of cocaine and saline was administered once per week as substitutes for the chronic dose.

*Phase 7: Assessment of Chronic Saline Administration (Drug Withdrawal) and Subsequent Dose Effects of Cocaine under the Correlated Schedule*

Each pigeon received daily presession administrations of saline upon completion of the chronic regimens. Daily presession administrations of saline continued for 61, 54, 63, and 56 sessions for Pigeons 3340, 3658, 6164, and 3578, respectively, after which each cocaine dose was tested. Weekly substitutions of a range of doses of cocaine (0.3, 1.0, 3.0, 5.6, and 10.0 mg/kg) were then administered again at least twice. The numbers of sessions required for these determinations were 124, 106, 121, and 147 for Pigeons 3340, 3658, 6164, and 3578, respectively.

*Behavioral Measures*

The main dependent measures calculated were index of curvature, overall responses per minute, average PRP, and head-in-hopper time. Overall response rate was calculated by dividing the total number of responses in a session by the total session time (minus feeder durations and timeouts). Average PRP was calculated by totaling all the pauses that occurred after food delivery, plus the latency to a response in the first interval of the session,



and then dividing the total by 10 (the total number of cycles in a session). The index of curvature describes deviations from a constant rate of responding (Fry, Kelleher, & Cook, 1960). The index was obtained using the cumulative total number of responses occurring in successive 48-s bins (i.e., 10ths of the interval). Dividing the interval into 10 bins allows the range of the possible indexes to fall between  $-.9$  and  $.9$ . In general, the higher the value of the index, the greater the degree of positive acceleration of responding across the interval. Values of the index approaching zero correspond to a lesser degree of curvature, with zero indicating no curvature or a constant rate. A negative index indicates a negatively accelerated curve. The index of curvature was selected because the measure is sensitive to, and directly quantifies, fluctuations in the patterns of responding depicted in cumulative records.

The head-in-hopper measure was determined by the amount of time the pigeon's head crossed the infrared beam located in the aperture while the hopper was raised. This measure became available during acute determination of the effects of cocaine during the correlated-schedule phase and thereafter. Head-in-hopper times were not obtained during the original baseline condition (FI 8 min without correlated contingencies).

## RESULTS

### *Behavioral Effects of Correlated Contingencies*

Figure 1 shows histograms of the index of curvature and rate of responding across the last 10 sessions of baseline and the last 10 sessions of the correlated-schedule phase before beginning drug testing for each pigeon. For Pigeon 3578, the data for one session were lost; therefore, only the last nine sessions of baseline are represented in this figure.

The effect of the correlated-schedule presentations on the index of curvature was negligible for all pigeons, as evidenced by the minimal change in that index across the two phases. Overall response rates generally were lower in the correlated-schedule conditions, yet these differences were not consistently maintained during the correlated-schedule condition (see the control rates in Table 2), except for Pigeon 6164.

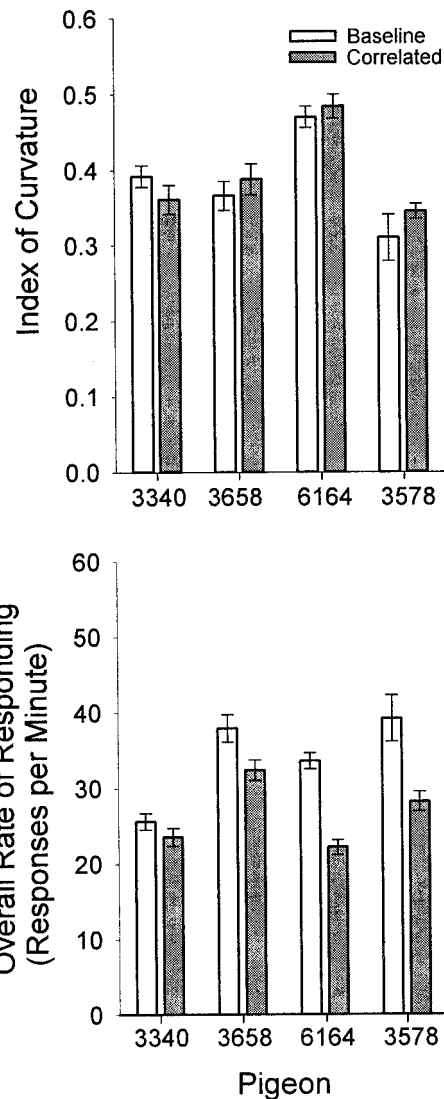


Fig. 1. Histograms of the index of curvature (top) and responses per minute (bottom) across the last 10 sessions of baseline (white bars) and correlated-schedule (gray bars) phases for each pigeon. Vertical lines extending from each bar represent the standard error of the mean.

Table 2 shows the index of curvature and responses per minute for each pigeon as a function of a range of doses of cocaine administered during baseline and the correlated-schedule condition. The presence of the correlated-reinforcement outcome produced no systematic difference in how cocaine altered response patterning across pigeons. Rates of responding under control (no-drug)

Table 2

Index of curvature and responses per minute across a range of doses of cocaine during FI 8-min (baseline, B) and correlated (C) FI 8-min schedules for each pigeon.

Pigeon	Index of curvature							Responses per minute						
	Con- trol	Saline	0.3	1.0	3.0	5.6	10.0	Con- trol	Saline	0.3	1.0	3.0	5.6	10.0
3340 B	.34	.36	.22	.18	.08	.04		42.46	40.98	49.43	49.18	65.01	12.93	
C	.36	.41	.24	.19	.09	.10		25.58	23.68	28.33	34.16	26.80	14.09	
3658 B	.29	.39	.17	.16	.16	.14		35.08	28.16	39.38	46.51	41.90	12.28	
C	.43	.37	.34	.23	.18	.20		30.43	35.31	33.90	39.13	40.67	17.13	
6164 B	.50	.50	.41	.35	.20	.22		39.77	37.01	45.86	49.38	19.05	0.76	0.01
C	.39	.39	.37	.22	.28	.20		18.16	11.94	23.41	25.91	18.98	5.78	0.10
3578 B	.29	.35		.16	.13	.11	.07	34.84	31.58		45.15	51.99	42.82	37.88
C	.33	.29	.26	.27	.21	.20	.02	27.22	25.26	33.90	30.56	38.40	29.46	7.36

conditions, however, decreased for all pigeons under the correlated schedule.

Based on the response criterion arranged for each feeder duration, if the correlated outcome exerted no effect it would be expected that the obtained durations would be approximately evenly distributed in thirds across the different durations. This was not the case; in fact, all 4 pigeons obtained a higher percentage of 2-s durations (50%, 42%, 67%, and 48% for Pigeons 3340, 3658, 6164, and 3578, respectively) than either 4- or 8-s durations. The percentage of 4- and 8-s durations obtained were approximately equal. These data reveal that there was a modest tendency for implementation of the correlated-schedule outcome to be followed by a decrease in the number of responses in the first half of the interval.

Figure 2 shows histograms of the average PRP in minutes and average total number of responses in the first half of the interval as a function of the preceding reinforcement duration for all pigeons during the last 10 sessions of the correlated schedule. These data illustrate that, for each pigeon, as reinforcement duration increased so did the average duration of the ensuing PRP, whereas the total number of responses that followed decreased.

#### *Effects of Chronic Cocaine*

Figure 3 shows the index of curvature, responses per minute, and head-in-hopper times as a function of dose of cocaine under acute and chronic dosing regimens for each pigeon under the correlated schedule of reinforcement. The dose-response functions

are from the initial chronic dosing regimen for Pigeons 6164 and 3578 (the 2 birds that experienced two doses chronically). Under conditions of acute administration of cocaine, the drug produced dose-related decreases in the index of curvature for each pigeon, with the performance of Pigeon 3578 being least sensitive to this effect. During chronic administration, the index-decreasing effects were attenuated for each pigeon, although the effect was evident at only the largest dose for Pigeon 3578. That is, tolerance developed to the index-decreasing and, therefore, the temporal pattern-disrupting effects of cocaine.

The middle row of Figure 3 shows number of responses per minute as a function of dose of cocaine. Acute dose-response functions were typically inverted U-shaped functions for each pigeon, with peaks in the curves at doses 1.0, 3.0, 1.0, and 3.0 mg/kg for Pigeons 3340, 3658, 6164, and 3578, respectively. At the lowest doses (0.3 or 1.0 mg/kg), number of responses per minute during the acute dosing regimen were approximately equal to rates during control and saline conditions for all pigeons. After chronic dosing, Pigeons 3340 and 3658 showed an attenuation of the rate-increasing effect after daily pre-session administration of cocaine and, for Pigeon 3658, the decrement at the largest dose was also eliminated. This effect was not observed for Pigeons 6164 and 3578; rather, number of responses per minute were higher at most doses after chronic cocaine delivery for these 2 pigeons.

The bottom row of Figure 3 shows the head-in-hopper time under each dose of co-

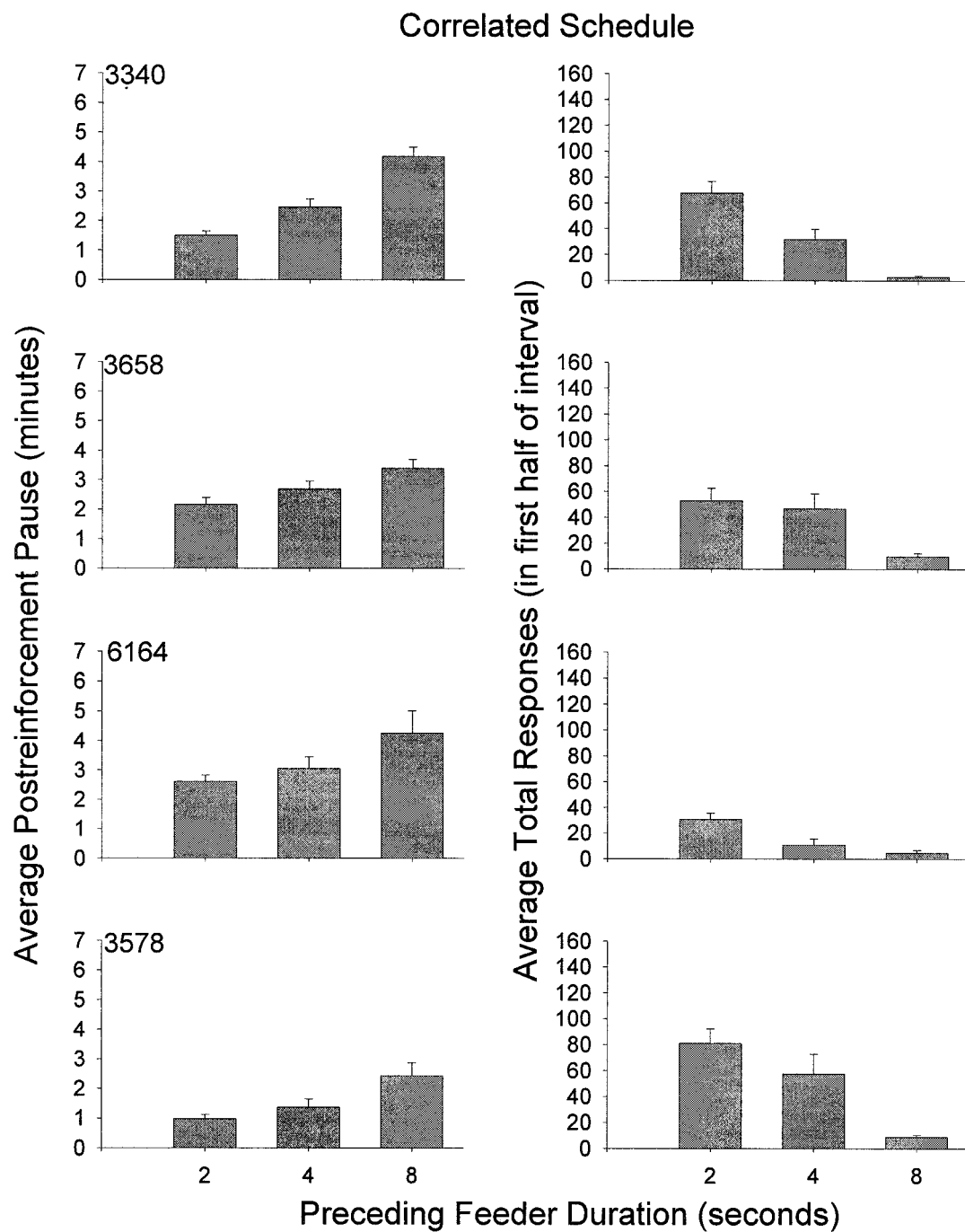


Fig. 2. Histograms of average PRP times (left column) and average total responses in the first half of the interval (right column) for each pigeon as a function of preceding reinforcement duration across the last 10 sessions of baseline. The standard error of the mean is represented by vertical lines extending from each bar.



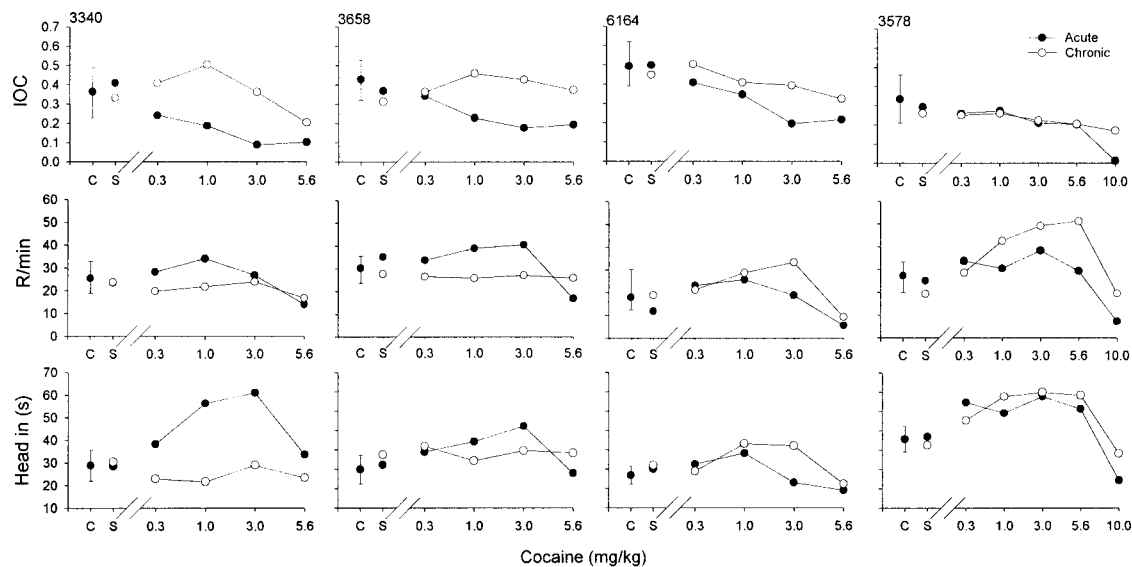


Fig. 3. Index of curvature (top row), mean responses per minute (middle row), and mean total head-in-hopper time (bottom row) for FI responding under conditions of behavior-correlated reinforcement magnitude and a range of doses of cocaine (0.3 to 10.0 mg/kg). Points above C show means from control sessions (i.e., those that immediately preceded sessions before which injections were given) and those above S are means from sessions preceded by injection of saline solution. Filled and open circles represent performance during acute and chronic dosing, respectively. Chronic doses were 1.0 mg/kg for Pigeon 6164 and 3.0 mg/kg for Pigeons 3340, 3658, and 3578. Vertical bars through the control-point means show the range of values.

caine for each pigeon. The means of two determinations of each dose are represented in the dose-response functions, although the data points for the index of curvature and response rates were the mean of three or four determinations of each dose (see Table 1). This is because the infrared beam used to measure head-in-hopper times was installed during the time that the acute dosing regimen was being conducted.

In general, head-in-hopper time increased during acute cocaine administration at low to moderate doses (0.3 to 3.0 mg/kg) for each pigeon relative to saline and control conditions. For 3 of the 4 pigeons, the increases were proportionally large, sometimes exceeding 100%. For Pigeon 6164, however, increases were smaller, both absolutely and relatively. In addition, there was a decreasing trend in these times at larger doses. During chronic administration, two patterns emerged: For Pigeons 3340 and 3658, increased head-in-hopper times were eliminated at intermediate doses, yielding flat dose-response functions. For Pigeons 6164 and 3578, cocaine at intermediate doses continued to increase head-in-hopper time.

Table 3 shows mean hopper-access times and ratio of head-in-hopper time to hopper-access time (session totals) across doses of cocaine and saline during acute and chronic dosing regimens of the correlated FI 8-min schedule. There was no systematic effect of dose on proportion of hopper-access time that a pigeon's head was in the hopper during determination of either acute or chronic effects. In general, actual head-in-hopper time corresponded well with obtained access time.

To summarize, similar effects on the index of curvature were obtained after chronic administration of cocaine to each pigeon (i.e., tolerance developed to the pattern-disrupting effects of cocaine), yet tolerance to the rate-increasing effects and increases in eating time were observed in only 2 pigeons (3340 and 3658). In general, the index of curvature is reduced as a function of increased responding early in the interval. Therefore, the only way that the index of curvature can increase during chronic administration with head-in-hopper times remaining elevated is if the dose also increases rates late in the interval. Figure 4 documents this effect. It shows scat-

Table 3

Mean food-access time in seconds and ratio of head-in-hopper time to access time (in parentheses) as a function of dose of cocaine during acute and chronic dosing under the correlated FI 8-min schedule.

Dose	3340		3658		6164		3578	
	Acute	Chronic	Acute	Chronic	Acute	Chronic	Acute	Chronic
Control	38.94 (.74)		38.44 (.52)		28.70 (.59)		42.70 (.84)	
Saline	35.33 (.81)	39.33 (.77)	51.00 (.44)	53.33 (.52)	28.00 (.72)	31.33 (.71)	47.33 (.78)	41.33 (.79)
0.3	52.66 (.73)	32.00 (.72)	52.00 (.56)	48.00 (.67)	34.00 (.66)	27.00 (.70)	61.33 (.89)	54.00 (.84)
1.0	63.00 (.90)	31.33 (.69)	64.50 (.53)	37.00 (.66)	49.33 (.70)	42.00 (.89)	54.40 (.90)	65.00 (.89)
3.0	64.50 (.95)	38.00 (.76)	70.50 (.60)	40.00 (.74)	47.33 (.28)	44.00 (.73)	70.66 (.82)	67.45 (.89)
5.6	42.00 (.80)	38.00 (.62)	40.50 (.45)	38.00 (.75)	28.50 (.32)	28.00 (.44)	64.00 (.80)	69.00 (.85)
10.0							35.33 (.41)	41.00 (.69)

ter plots of the logarithm of the number of responses in each 48-s bin during acute dosing (i.e., each 8-min interval was divided into 10 equal bins within which the number of responses were collected across a session) over the logarithm of number of responses in the corresponding bin under control (no-drug) conditions. In general, the number of responses increased across the interval as documented by the baseline values of the index of curvature (see Figure 3). Points on the left side of the graphs represent responding early in the interval when rates were generally low under no-drug conditions, and points on the right side represent late-interval responding. The number of responses during cocaine administration was based on acute effects of the dose of cocaine that later was delivered chronically: 3.0 mg/kg for Pigeons 3340, 3658, and 3578 and 1.0 mg/kg for Pigeon 6164. Points from all administrations are represented by filled circles. The positive diagonal represents the point at which these response counts would be equal (i.e., the line of no effect). Elevated numbers of responses under drug conditions are represented by points above the positive diagonal line, whereas decrements in number of responses under drug conditions are indicated by points below the diagonal line.

For Pigeons 3340 and 3658, the pattern of points crosses over the diagonal, indicating response-rate decrements (compared to control levels) at the end of the interval following acute administration. The distributions of responding across bins for Pigeons 6164 and 3578 follow a different pattern: The filled points (from acute effects of the first chronic dose) generally lie above the positive diago-

nal and do not cross over it. Thus, the number of responses at the end of the interval were approximately the same as or higher than the number of responses under control (no-drug) conditions. Doses for a second chronic dosing regimen for Pigeons 6164 and 3578 were therefore selected based on the smallest acute dose that produced lower counts at the end of the interval, similar to the effect observed for Pigeons 3340 and 3658. The doses that produced this effect for Pigeons 6164 and 3578 were 3.0 and 10.0 mg/kg, respectively, and their effects are illustrated by the open circles.

Figure 5 shows the index of curvature, number of responses per minute, and head-in-hopper times as a function of doses of cocaine for Pigeons 6164 and 3578 under the second chronic dose. For both pigeons, the attenuation of the index-decreasing effect of acute cocaine remained evident. For Pigeon 6164, the dose-response function for response rate under the second chronic dose (3.0 mg/kg) was similar to the acute dose-response function. The function was shifted slightly to the right, however, an indication of modest tolerance. For Pigeon 3578, by contrast, after the second chronic dose (10.0 mg/kg) was administered, the functions for both rate and head-in-hopper times showed an attenuation of increases at smaller doses and decreases at larger doses, a pattern that is similar to that of Pigeon 3658 (see Figure 3).

Figure 6 shows representative cumulative records under the correlated-schedule condition. Note that the records for Pigeons 6164 and 3578 show the effects of the second chronic dose (see below), the dose that pro-

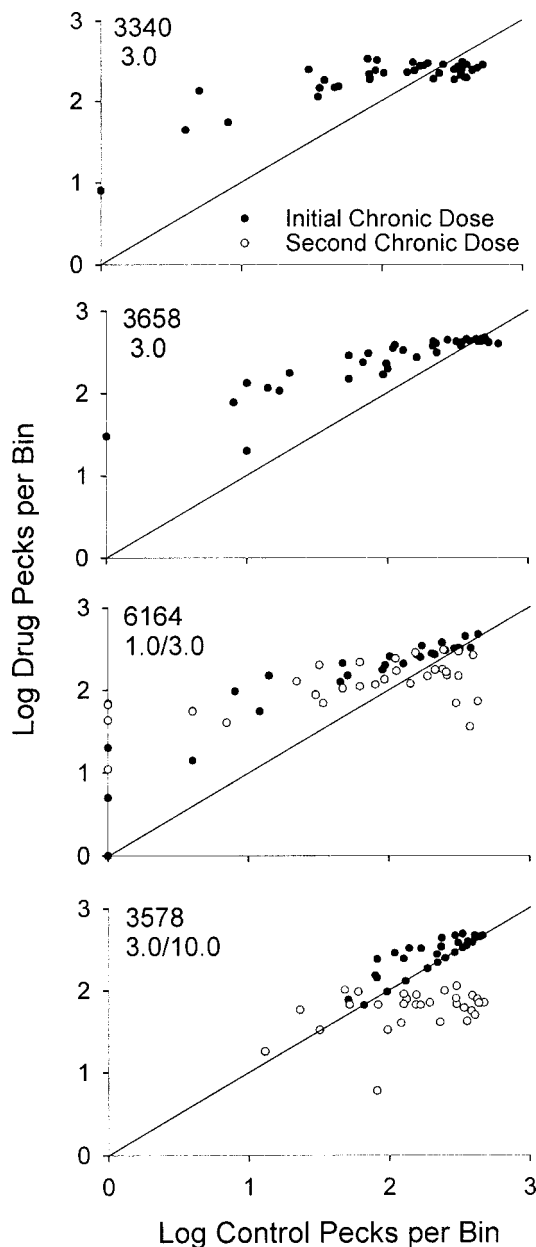


Fig. 4. Rate-dependency scatter plots during acute dosing under the correlated schedule for each pigeon. The common logarithm of number of responses in each 48-s segment (bin) of the FI following drug administration (10 bins per FI component) is plotted against the logarithm of control (no-drug) number of responses in the corresponding bin. The positive diagonal indicates when response counts during drug and no-drug conditions would be equivalent. Filled circles show the acute effects of a single dose of cocaine. Acute doses were 3.0 mg/kg for Pigeons 3340, 3658, and 3578 and 1.0 mg/kg for Pigeon 6164. Open circles display, for 2 pigeons, effects of the smallest acute dose that produced reduced counts at the end of the interval. These doses were 3.0 and 10.0 mg/kg for Pigeons 6164 and 3578, respectively.

duced effects most similar to those seen in the other 2 pigeons. Under saline administration, characteristic FI performance was observed throughout each session. Rates were generally low or zero early in most intervals, after which a transition to higher rates occurred. The records for all 4 pigeons showed increased responding early in (i.e., the first half of) each interval following acute cocaine relative to responding under saline. Increases in overall rate are evident for Pigeons 3340, 3658, and 6164. Again, the effects were fairly consistent across a session. After chronic administration of cocaine, response patterning more closely resembled performance under pre-session saline deliveries than performance during acute (i.e., occasional) administration of that same dose, with Pigeons 6164 and 3578 showing elevated overall rates compared to baseline and acute effects.

#### *Effects during Chronic Saline Administration*

Figure 7 shows the index of curvature, response rates, and head-in-hopper time as a function of cocaine doses after more than 50 sessions of chronic saline administration (i.e., after withdrawal from cocaine) under the correlated-schedule condition. The original acute dose-response functions for the correlated schedule are provided for comparison. For each pigeon, the index of curvature remained high following cocaine administration. That is, the dose-response functions obtained during chronic saline administration were similar to the functions obtained during chronic cocaine delivery (cf. Figure 3). The period of time without daily cocaine, therefore, did not result in any loss of tolerance to the effects of the drug on temporal patterning.

The middle row shows response rate as a function of a range of doses of cocaine after the drug was withdrawn, again with the acute function for comparison. Comparison of the postwithdrawal functions to those obtained during the chronic drug regimens (Figures 3 and 6) reveals little change in overall rates of responding.

The bottom row shows head-in-hopper time across a range of doses of cocaine for each pigeon during the acute and postwithdrawal conditions. As with index of curvature and response rate, head-in-hopper times dur-

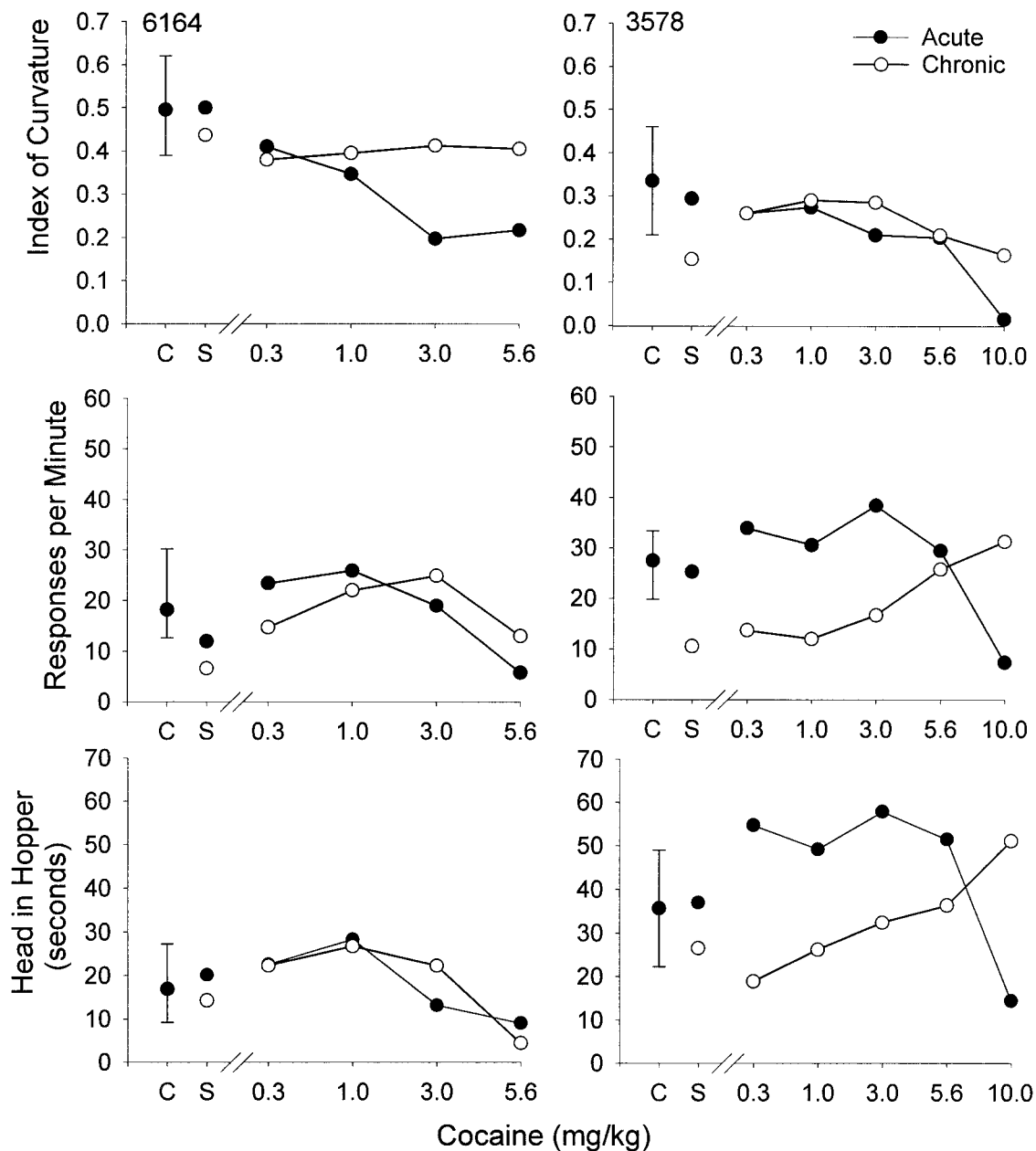


Fig. 5. Dose-response functions for Pigeons 6164 and 3578 after the chronic doses were increased to 3.0 mg/kg and 10.0 mg/kg, respectively, for index of curvature (top row), responses per minute, and head-in-hopper time in seconds (bottom row). For all functions, filled circles represent mean values under conditions of acute administration. Open circles show the mean values at a range of doses of cocaine tested during exposure to the second chronic dose. Other details are as in Figure 3.

ing chronic saline delivery were not similar to acute head-in-hopper times but were similar, instead, to the functions obtained during chronic cocaine delivery (Figures 3 and 6).

## DISCUSSION

The results of the current experiment, with respect to its five original purposes, suggest

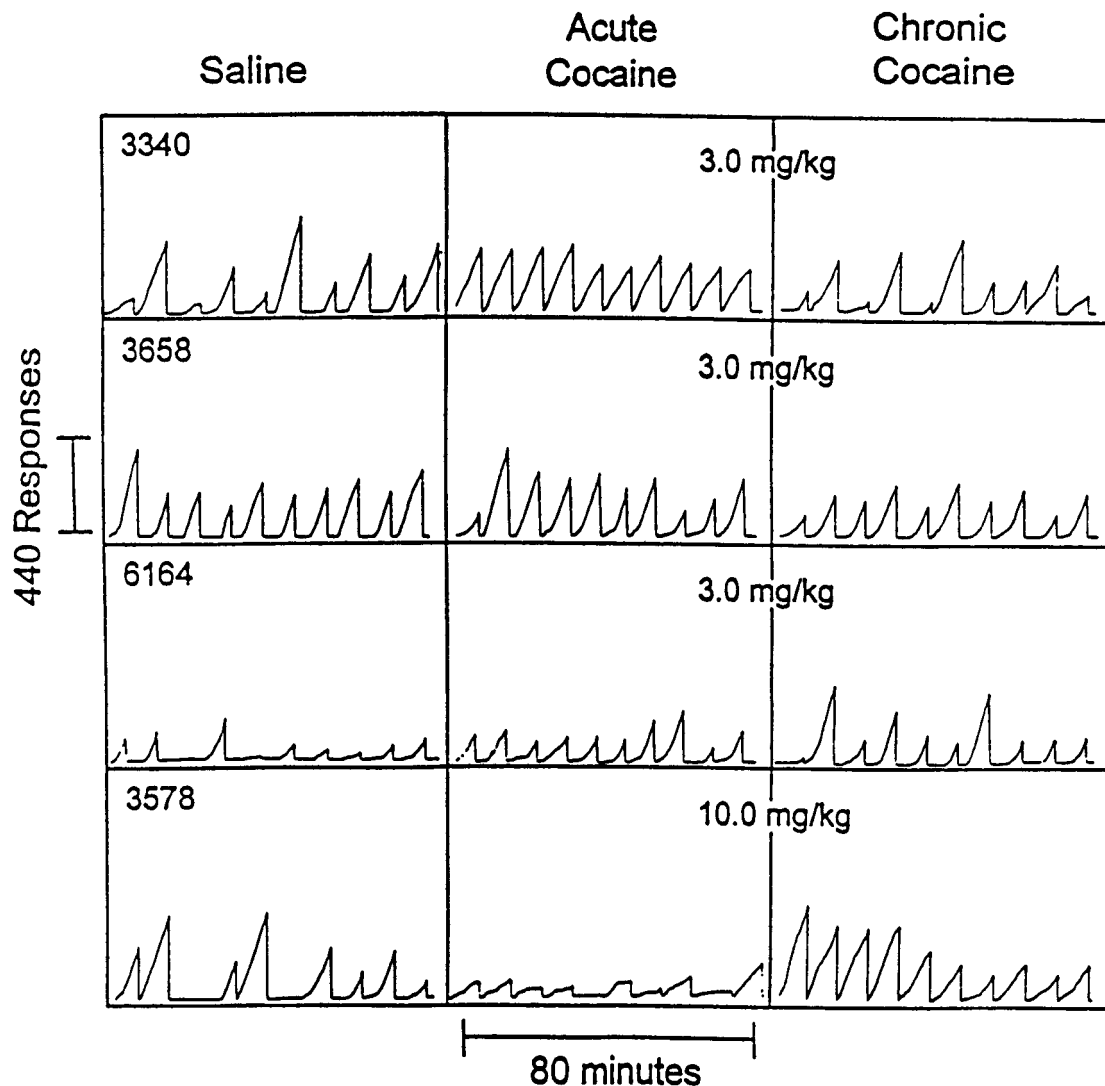


Fig. 6. Cumulative records for pigeons' key pecking under a correlated schedule of reinforcement. One session is approximately 80 min, which is represented on the x axes; cumulative responses are located on the y axes. The pen reset at each food delivery, and the recorder did not operate during postfood timeouts. The records in the left column depict performance under conditions of saline administration. Those in the center column show response rates and patterns under acute dosing with the dose that was later used in the chronic condition. The records in the right column are from sessions during daily pre-session (i.e., chronic) administration of cocaine. Records for Pigeons 3340 and 3658 represent performance during the initial chronic dosing conditions (with a dose of 3.0 mg/kg delivered to each pigeon); performance under the second chronic dose (3.0 mg/kg and 10.0 mg/kg) for Pigeons 6164 and 3578 is displayed in these records.

the following: (a) A procedure was developed in which cocaine administration increased the amount of grain obtained; (b) the addition of a correlated outcome to an FI schedule had only modest effects on performance; (c) the effects of acute cocaine administration under the correlated schedule were sim-

ilar to those observed with the simple FI schedule; (d) cocaine, at appropriate doses, increased the amount of food obtained and also engendered rate-dependent effects; and (e) enhanced access to food was lost as tolerance developed to the effects of the drug. That is, the reinforcement gain that resulted



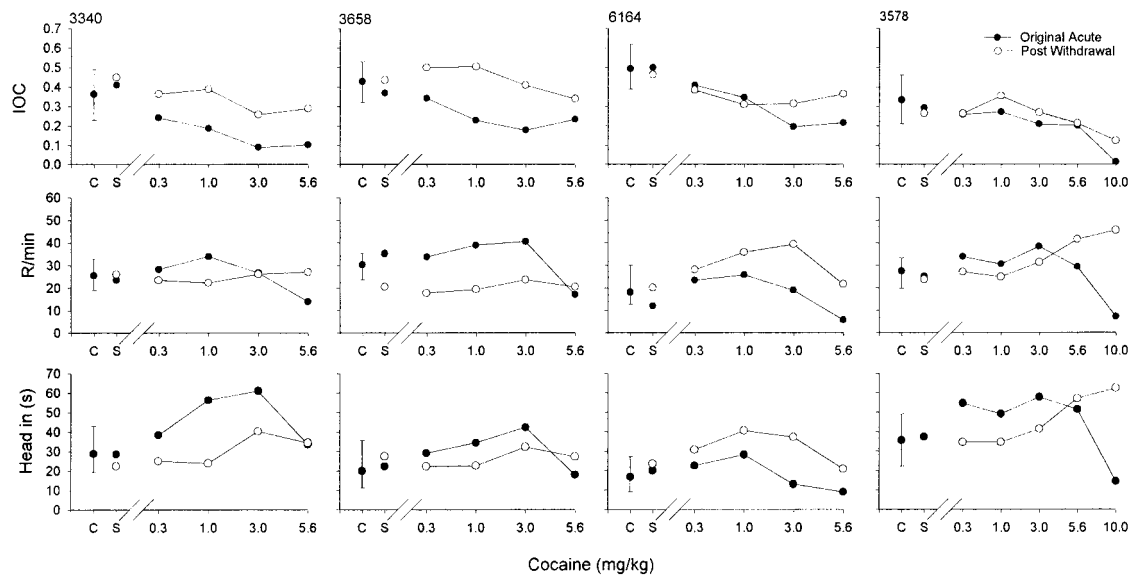


Fig. 7. Index of curvature (top row), mean responses per minute (middle row), and head-in-hopper time in seconds (bottom row) as a function of dose of cocaine for all pigeons during acute and postwithdrawal chronic saline delivery. Filled circles represent the values obtained during acute delivery of cocaine, and the open circles depict values during chronic saline administration after cocaine withdrawal. Other details are as in Figure 3.

from acute cocaine administration apparently was not sufficient to prevent the development of tolerance when the drug was given repeatedly.

#### *Effects of Correlated Contingencies on FI 8-Min Performance*

The effects of the correlated outcomes used here on overall rates of responding under an FI schedule were not consistent with earlier studies that found that response rates were sensitive to reinforcer magnitude (Dodd, 1980; Gentry & Eskew, 1984; cf. Figure 1) under correlated-schedule outcomes. Essentially, minimal changes in rates occurred following implementation of the contingency on responding early in the interval. If anything, rates early in the interval decreased, as evidenced by the increase in frequency of 2-s feeder durations. This is a result in the opposite direction than one would predict from the arranged outcome. In addition, response patterning, assessed by the index of curvature (Fry *et al.*, 1960), showed essentially no difference from baseline to correlated-schedule conditions (Figure 1). This lack of sensitivity to correlated outcomes can most likely be attributed to the choice of schedule parameters. For example, Gentry and Eskew

employed a procedure wherein each response during an 8-s automaintenance trial produced greater access time to reinforcement. Similarly, Dodd used a behavior-correlated schedule with 8-s stimulus periods and found that the median number of responses increased or decreased when reinforcement rate was contingent upon high or low rates, respectively. In the present experiment, different rates of responding in a 4-min interval were followed by access to different amounts of grain 4 min later. This may have influenced the results of the present findings in two ways: (a) The delay between the "response" and the delivery of the reinforcer was such that a reinforcement relation was not established, or (b) the size of the putative behavioral unit (*i.e.*, rates of responding in a 4-min interval) to be reinforced may have been too large.

In addition to schedule parameters, the sensitivity of performance to correlated outcomes may be dependent on the unit of behavior under investigation. For example, Hendry (1962) investigated the effect of correlated reinforcement on FI performance. The length of the terminal interresponse time (IRT) determined the amount of reinforcement to be delivered to the pigeons.

The results suggested that the terminal IRT was sensitive to the magnitude of reinforcement delivered immediately upon completion of the IRT. Although Hendry also used an FI 8-min schedule, the outcome differed with respect to both how much behavior contributed to the outcome and the delay between the behavior and its reinforcing consequences. Whereas Hendry arranged for the delivery of the reinforcer within close temporal contiguity to the reinforced response (i.e., immediately, without delay to reinforcement), this relation did not exist with the correlated-schedule outcomes of the present experiment.

The outcome used here, however, was not entirely without effect on performance. During the behavior-correlated schedule, PRP and overall rate of responding as a function of preceding feeder duration were systematically related for each pigeon (Figure 2). For example, high average rates of responding, and, concomitantly, short PRPs were observed after the presentation of 2-s access to grain. The inverse was observed (i.e., PRP was longer and rates were lower as the duration of the feeder cycle increased) immediately after the presentation of 8-s access to grain. When 4-s access to grain was available, intermediate rates of responding and PRP values were observed. These findings illustrate that the differences in feeder durations were sufficient to influence some aspects of performance, even though they did not alter overall response rates or index of curvature. These effects also permit a reconciliation between the finding of more short reinforcer durations yet no change in the index of curvature. Short feeder durations were followed by higher rates and shorter PRPs, which should decrease the index of curvature. The effects were apparently offset by the increase in pausing that followed long-duration reinforcers, so that the average curvature was not changed.

The relation between pause duration and immediately preceding feeder duration is similar to results obtained by Staddon (1970). Pigeons' key pecking was maintained on an FI 60-s schedule of reinforcement, and different magnitudes of reinforcement (i.e., 1.3, 2.4, 3.5, 5.7, and 9.0 s of access to grain) were delivered randomly upon completion of each interval. A linear relation was found between

PRP and the preceding reinforcement duration: As the magnitude of reinforcement increased, PRP also increased. The inverse was observed with response rates: As reinforcer duration increased, rates decreased.

#### *Effects of Acute Administration of Cocaine on Correlated-Schedule Performance*

Because the presence of the correlated outcome yielded no systematic effect on response rates or index of curvature, it is not surprising that it was apparently also without effect when cocaine was given acutely (see Table 2). Disruptions in response patterning, in the form of increased responding in the first half of the interval with index of curvature values approaching zero as dose of cocaine increased, occurred during acute administration of cocaine for each pigeon when the correlated schedule was in effect (see Figures 3 and 5).

With correlated-schedule outcomes in effect, acute administration of intermediate doses of cocaine increased grain delivery for each pigeon. This resulted from higher rates of responding in the first half of the interval relative to baseline (Figure 5); thus, one of the goals of the procedure was achieved. The finding of increased rates early in the interval is consistent with findings that *d*-amphetamine and other sympathomimetic amines have been shown to increase responding early in the interval (e.g., Branch & Gollub, 1974; McMillan, 1968a, 1968b, 1969). Each pigeon therefore received more access to food when certain doses of cocaine were administered. Increased availability of food was accompanied by increased times spent with the head in the hopper.

#### *Effects of Chronic Administration of Cocaine During the Correlated-Schedule Condition*

After chronic administration of cocaine, a shift upwards or to the right in the dose-response function for index of curvature was observed for each pigeon (Figure 3). Thus, tolerance occurred to the pattern-disrupting effects of cocaine. This effect was observed at every dose that was initially effective for each pigeon. Furthermore, with repeated pre-session (i.e., chronic) dosing, response patterning came to resemble more closely that seen during control (i.e., saline) conditions than records from the initial exposure (i.e., acute

dosing) of that same dose of cocaine (Figure 5). Attenuation of the pattern-disrupting effects was observed for each pigeon. Increases in rates of responding and head-in-hopper times engendered by acute cocaine administration were diminished after daily pre-session administration for 2 pigeons (3340 and 3658), but the other 2 pigeons (6164 and 3578) did not show evidence of tolerance to increased rates or head-in-hopper times after chronic cocaine administration (Figure 3 and Table 3). The ratios of head-in-hopper time to the total duration of grain availability during control conditions were .74, .52, .59, and .84 for Pigeons 3340, 3658, 6164, and 3578, respectively. Whether cocaine delivery was acute or chronic, this proportion remained relatively constant across cocaine doses (Table 3). The one noteworthy exception is in the data for Pigeon 6164. At the 3.0 mg/kg dose, acute cocaine resulted in a diminished "efficiency" of eating, with the pigeon keeping its head in the hopper for only an average of 28% of the available time. For the other 3 pigeons, such notable decrements were absent. Following chronic administration, Pigeon 6164 was considerably more efficient, keeping its head in the hopper an average of 73% of the available time.

Analysis of the rate-dependency plots (the log-log plots of responses in portions of the interval) for the dose that was delivered chronically reveals a correlation between effects on patterning and whether tolerance developed to rate and head-in-hopper measures (Figure 4). For the 2 pigeons (3340 and 3658) that showed tolerance to effects on head-in-hopper time and response-rate increases, a reduced number of responses at the end of the interval occurred when the chronic dose of cocaine had been given acutely. For the other 2 pigeons (6164 and 3578), which showed tolerance to the pattern-disruptive effects but not for response rate or head-in-hopper time, the number of late-interval responses was not reduced (Figure 4). When a dose that reduced the number of responses at the end of the interval was subsequently administered chronically, tolerance was observed across all measures for Pigeon 3578, and the data for Pigeon 6164 became more similar to those of the other 3 pigeons. Whether tolerance developed to particular aspects of performance, therefore,

appeared to be related to the character of the acute effect of the dose given chronically.

Why the correlation between acute effect on rates across the interval was related to whether tolerance developed to rate and eating-time measures remains unclear. Especially puzzling is why decreased responding near the end of the interval appears to be crucial. Responding at that time played no role in the correlated outcome. The finding, however, that dose was an important determinant of tolerance adds to the growing body of evidence implicating dose as crucial in determining whether tolerance occurs to the effects of cocaine on behavior (cf. Bowen, Fowler, & Kallman, 1993; Stafford & Branch, 1996; Woolverton, Kandel, & Schuster, 1978).

When daily cocaine administration was terminated, and after saline was delivered chronically for more than 50 days, the dose-response functions for index of curvature, response rate, and head-in-hopper times were more similar to the functions obtained during chronic cocaine administration for all pigeons than they were to the acute dose-response functions (see Figures 3, 5, and 7). Tolerance that had developed during the chronic drug regimen persisted well after drug withdrawal.

The persistence of tolerance across such a long period is consistent with evidence showing that experience with cocaine can produce effects, both neurochemical and behavioral, that persist long after exposure (e.g., Lipton & Ellison, 1992; Ziegler, Lipton, Toga, & Ellison, 1991), and extends such findings to pigeons. The observations of the present study also extend the findings of Stafford, Branch, and Hughes (1994), who found that once tolerance had developed to the effects of cocaine on operant performance, it was maintained for several months. In that study, injections of a test dose, which may have functioned as "booster" or "reminder" administrations, were given every 16 days. In the present study, tolerance was evident even though no drug was experienced for approximately 2 months.

It may be useful to consider the persistence of tolerance as reflecting stimulus control of cocaine over responding. If this were the case, then one would expect little decrement in stimulus control over the long period in which the main controlling stimulus (i.e., the

cocaine "cue") is absent. This was observed in the present study (Figure 7) and points to the possibility of using behavioral procedures that weaken stimulus control to counter long-term effects of cocaine exposure. Future research could be focused on that issue.

The present results are consistent with those of Branch et al. (1998), in that tolerance was observed under conditions of increased access to grain. In the Branch et al. study, pigeons' key pecking was maintained on a relatively large FR schedule. Acute administration of cocaine increased the rate of responding and, therefore, increased the rate of food presentations. After chronic administration, tolerance to the rate-increasing effect of cocaine was observed.

These results are not consistent, however, with those of Schuster et al. (1966), who found that tolerance developed when there was a loss of reinforcement under conditions of chronic drug administration but not when reinforcement was increased. In their study, however, negative reinforcement was increased (cf. Smith, 1990), whereas positive reinforcement was increased in the present study. Whether the difference is due to the distinctions in type of reinforcement remains to be determined. It remains unclear, then, under what conditions a drug effect that increases reinforcement will show tolerance during chronic administration.

One of the goals of the present set of experiments was to develop a procedure in which drug administration produced an increase in grain delivery for each pigeon. In that, we succeeded (see acute functions in Figure 3). However, the present research provides no evidence that the obtained increases in amount of food obtained were of the sort that acted as reinforcement in the outcome that was arranged (Figure 1 and Table 2). That is, technically speaking, we achieved not reinforcement gain but merely a gain in food obtained. The challenge remains, therefore, to develop procedures that can reliably produce reinforcement gain when behaviorally active drugs are administered.

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